ARTÍCULO ORIGINAL

Validación externa de ecuaciones de riesgo cardiovascular en el Cono Sur de Latinoamérica: ¿cuál predice mejor?

External Validation of Cardiovascular Risk Scores in the Southern Cone of Latin America: Which Predicts Better?

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RESUMEN

Introducción: La estimación inexacta del riesgo cardiovascular poblacional puede llevar a un manejo inadecuado de las intervenciones médicas preventivas, como, por ejemplo, el uso de estatinas.
Objetivo: Evaluar la validez externa de ecuaciones de predicción de riesgo cardiovascular en población general del Cono Sur de Latinoamérica.
Material y métodos: Se evaluaron ecuaciones que incluyen variables evaluadas en el estudio CESCAS y que predicen tanto morbilidad como mortalidad cardiovascular global (CUORE, Framingham, Globorisk y Pooled Cohort Studies Equations). Para cada ecuación se realizó un análisis independiente en el que se tuvieron en cuenta los eventos cardiovasculares relevados. Se evaluó la discriminación de cada ecuación a través del cálculo del estadístico-C y el índice Harrell C. Para evaluar la calibración se graficó la proporción de riesgos observados vs. estimados por quintilos de riesgo para cada ecuación y se calculó la pendiente β de regresión lineal para las estimaciones. Se calculó sensibilidad y especificidad para la detección de personas con elevado riesgo cardiovascular.
Resultados: La mediana del tiempo de seguimiento de la cohorte al momento del análisis es de 2,2 años, con un rango intercuartilo de 1,9 a 2,8 años. Se incorporaron a los análisis 60 eventos cardiovasculares. Todos los valores de estadístico-C y del índice de Harrell fueron superiores a 0,7. El valor de la pendiente β más alejado de 1 fue el de Pooled Cohort Studies Euations.
Conclusiones: Si bien los parámetros de validación externa evaluados fueron similares, CUORE, Globorisk y el índice de Framingham fueron las ecuaciones con mejores indicadores globales de predicción de riesgo cardiovascular.

Palabras claves: Enfermedad cardiovascular - Factores de riesgo - Evaluación del riesgo - Prevención.

ABSTRACT

Background: Inaccurate estimates of demographic cardiovascular risk may lead to an inadequate management of preventive medical interventions such as the use of statins.
Objectives: The aim of this study was to evaluate the external validity of cardiovascular risk equations in the general population of the Southern Cone of Latin America.
Methods: Equations including variables evaluated in the CESCAS cohort study and that estimate overall cardiovascular mortality (CUORE, Framingham, Globorisk and Pooled Cohort Studies) were assessed. For each equation, an independent analysis was performed taking into account the cardiovascular events originally considered. Discrimination of each equation was evaluated through C-statistic and Harrell's C-index. To assess calibration, a graph was built for each equation with the proportion of observed events vs. the proportion of estimated events by risk quintiles and the β slope of the resulting linear regression was calculated. Sensitivity and specificity were determined for the detection of people at high cardiovascular risk.
Results: The median follow-up time of the cohort at the time of the analysis was 2.2 years, with an interquartile range of 1.9 to 2.8 years. Sixty cardiovascular events were incorporated into the analysis. All C-statistic and Harrell's-C index values were greater than 0.7. The value of the β slope farthest from 1 was that of the Pooled Cohort Studies score.
Conclusions: Although the external validation parameters evaluated were similar, CUORE, Globorisk and the Framingham equations showed the best global performance for cardiovascular risk estimation in our population.

Key words: cardiovascular disease - Risk factors, risk assessment, prevention

Abreviaturas

CV	Enfermedad cardiovascular	**RCV**	Riesgo cardiovascular

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INTRODUCCIÓN

La enfermedad cardiovascular (CV) es la causa de muerte dominante tanto en el mundo desarrollado como en vías de desarrollo. Aproximadamente, el 80% de las muertes de causa CV se produce en países de bajos y medianos ingresos. (1, 2) El estudio INTERHEART mostró que 9 factores de riesgos medibles y potencialmente modificables, son responsables del 90% de los infartos agudos de miocardio. (3) La mayoría de dichos factores de riesgo cardiovascular representan, además, las principales causas de carga de enfermedad en el mundo. (4) Es crítico que los países en vías de desarrollo incrementen los esfuerzos con objeto de perfeccionar la capacidad para la detección de individuos de elevado riesgo cardiovascular (RCV) quienes se beneficiarían de intervenciones médicas más intensas.

Durante los últimos años, la estimación del RCV ha asumido un papel central en la prevención cardiovascular primaria y, así, la investigación en el campo de la predicción de riesgo se ha convertido en materia fuerte de estudio. (5) La estimación del RCV futuro no solo facilita el manejo clínico global como base para la toma de decisiones terapéuticas a nivel individual, sino también como herramienta para la evaluación del perfil de riesgo a nivel poblacional. (6) Las decisiones en prevención CV deberían ser tomadas luego de una adecuada estimación del RCV. Ejemplo de esto último, es el uso de tratamiento médico con estatinas en aquellos individuos en los que se detecta un RCV elevado. (7) A su vez, el cálculo del RCV no solo constituye una herramienta de soporte esencial para la toma de decisiones clínicas, sino también colabora para la comunicación y transmisión de información a los pacientes. (5)

Los índices de predicción de RCV son herramientas prácticas de fácil uso en el primer nivel de atención. La mayoría de los modelos de predicción de RCV han sido elaborados en países desarrollados utilizando bases de datos de poblaciones con realidades socio-demográficas, epidemiológicas y nutricionales diferentes a las de regiones como la del Cono Sur de Latinoamérica. (5) En relación con esto, la predicción inexacta del riesgo puede llevar al inadecuado inicio de intervenciones médicas en individuos con riesgo real menor que el predicho por ecuaciones de predicción creadas en poblaciones distintas. (8, 9)

El objetivo de este estudio es evaluar la validez externa (calibración, discriminación, sensibilidad y especificidad) de ecuaciones de predicción de RCV elaboradas en países desarrollados, en los primeros datos de seguimiento de la cohorte CESCAS, una muestra representativa de población general de cuatro ciudades del Cono Sur de Latinoamérica (Argentina, Chile y Uruguay). Para nuestro conocimiento, este es el primer estudio que evalúa y compara diferentes ecuaciones de predicción de RCV en poblaciones pertenecientes al Cono Sur de Latinoamérica. (9-11)

MATERIAL Y MÉTODOS

Ecuaciones de predicción seleccionadas

La selección de las ecuaciones de predicción de RCV fue realizada sobre la base de los modelos presentados en la guía Europea 2016 sobre prevención cardiovascular en la práctica clínica. (12) Las ecuaciones incluidas para el análisis fueron seleccionadas siguiendo dos pasos. Primero se incluyeron aquellos modelos de predicción cuyas variables hubieran sido todas evaluadas por la cohorte CESCAS del Cono Sur de Latinoamérica y, luego, finalmente, se excluyeron aquellas ecuaciones que solo predicen mortalidad CV o solo eventos coronarios. Los modelos evaluados fueron: ASSIGN-SCORE, (13), QRISK1 (14) & QRISK2, (15) SCORE, (16) PROCAM, (17) Pooled Cohort Studies Equations, (18) Framingham, (19) CUORE (20) y Globorisk. (21) Las ecuaciones seleccionadas para ser evaluadas fueron las últimas cuatro nombradas, el proceso de selección se grafica en la Figura 1. En la Tabla 1, se describen los eventos finales que predice cada una de estas ecuaciones, las variables incluidas en los modelos y los rangos de edad que evalúan.

La cohorte CESCAS

Los detalles del diseño y método de muestreo del estudio de cohorte CESCAS ya han sido publicados previamente. (22, 23) En resumen, CESCAS es un estudio de cohorte prospectiva

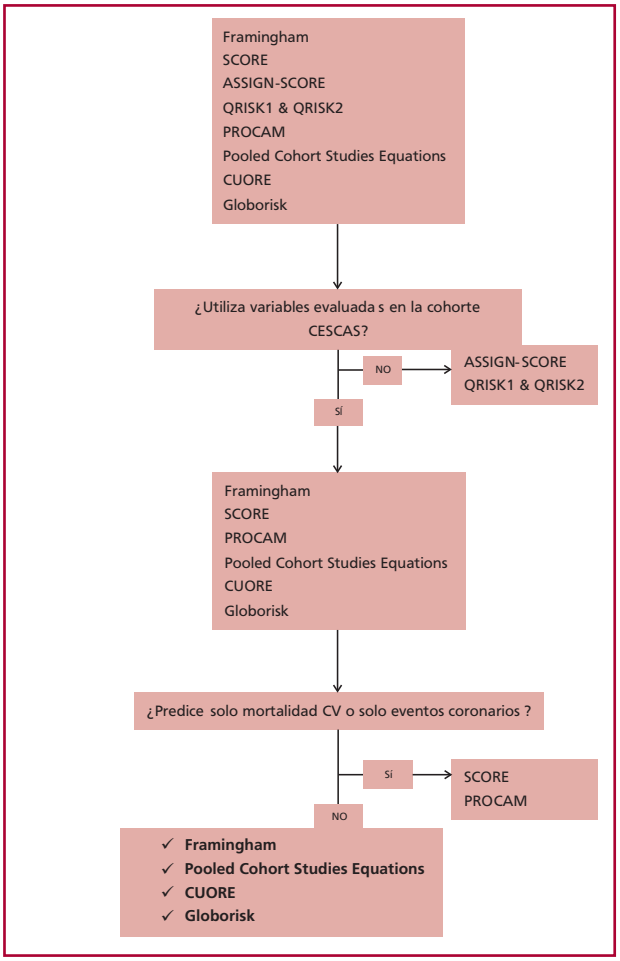


Fig. 1. Proceso de selección de las ecuaciones de RCV para evaluar.

Tabla 1. Características de los modelos evaluados¥

	Cuore	Framingham	Globorisk	Pooled Cohort Studies Equations
Variables incluidas en los modelos	Sexo	Sexo	Sexo	Sexo
	Edad	Edad	Edad	Edad
	Colesterol total	Colesterol total	Colesterol total	Colesterol total
	c-HDL	c-HDL	–	c-HDL
	TBQ	TBQ	TBQ	TBQ
	PAS	PAS	PAS	PAS
	–	DBT	DBT	DBT
	Tratamiento antihipertensivo	Tratamiento antihipertensivo	–	Tratamiento antihipertensivo
Rango de edad	35-69	30-75	40-84	20-79

¥ TBQ: Tabaquismo. PAS: Presión arterial sistólica. DBT: diabetes. IAM: Infarto agudo de miocardio. ACV: Accidente cerebrovascular. EAP: Enfermedad arterial periférica. IC: Insuficiencia cardíaca.

con base poblacional de 7524 adultos (3165 hombres y 4359 mujeres) de entre 35 y 74 años, los cuales fueron reclutados entre diciembre 2010 y diciembre de 2012. La muestra proviene de un muestreo polietápico representativo de la población general de cuatro ciudades del Cono Sur de Latinoamérica: Bariloche y Marcos Paz (Argentina), Temuco (Chile) y Canelones (Uruguay). La tasa global de respuesta fue del 73,4% y fue similar en hombres y mujeres en todos los sitios.

Los datos del estudio fueron recolectados durante una visita al hogar y una a un centro médico. Durante la encuesta en el hogar se recolectó información socio-demográfica como edad, sexo, educación y ocupación. Las medidas antropométricas fueron obtenidas por observadores entrenados y certificados utilizando protocolos y técnicas estandarizadas. La presión arterial se obtuvo con el participante en posición sentado luego de 5 minutos de reposo utilizando un tensiómetro aneroide o de mercurio estándar, se utilizó para el análisis el promedio de tres mediciones. Peso corporal, altura y circunferencia de cintura se midieron dos veces durante la evaluación y el promedio de las dos mediciones se utilizó en todos los análisis.

Una muestra de sangre en ayunas fue obtenida para las mediciones bioquímicas de lipoproteínas, creatinina y glucemia. La duración del ayuno fue verificada antes de la obtención de la muestra, no se obtuvo la muestra si el ayuno era inferior a 10 horas. Glucemia, colesterol total, colesterol HDL, triglicéridos y creatinina se evaluaron por métodos estándar. La concentración de colesterol LDL se calculó utilizando la ecuación de Friedewald en caso que los triglicéridos hubieran sido inferiores a 400 mg/dL. (24) La diabetes se definió como glucemia ≥ 126 mg/dL o autorreporte de antecedente de diabetes o tratamiento actual con insulina o hipoglucemiantes orales.

Los eventos cardiovasculares (angina, infarto agudo de miocardio fatal y no fatal, ACV fatal y no fatal, revascularización coronaria/carotidea/periférica, insuficiencia cardíaca y muerte súbita) en esta primera ronda de seguimientos fueron confirmados por médicos especialistas en clínica médica o cardiólogos luego de verificar la documentación correspondiente al evento. Es de destacar que la cohorte CESCAS no relevó claudicación intermitente, uno de los puntos finales de la ecuación de Framingham.

Análisis estadístico: Validación externa de los modelos

Para cada ecuación seleccionada se obtuvieron los coeficientes de regresión de las publicaciones originales. Junto con dichos coeficientes, todas las ecuaciones se recalibraron a la población de CESCAS utilizando la siguiente ecuación exponencial: (19)

$$\hat{p} = 1 - S_0(t)^{\exp(\sum_{i=1}^{p} \beta_i x_i - \sum_{i}^{p} \beta_i \bar{x}_i)}$$

Donde $S_0(t)$ es la sobrevida al tiempo de seguimiento considerado; β_i son los coeficientes de regresión estimados (*Log hazard ratio*); X_i es el valor específico de cada uno de los factores de riesgo considerados por la ecuación, $\bar{X}_i$ se refiere a los valores promedios de cada uno de los factores de riesgo en la población basal de CESCAS y p se corresponde con el número de factores de riesgo de cada una de las ecuaciones.

Se creó en la base de datos una variable "punto final" diferente para cada una de las ecuaciones (Tabla 1), incluidos específicamente los eventos para los cuales fueron diseñadas como herramienta de predicción.

La *discriminación* de cada una de las ecuaciones se evaluó a través del cálculo del estadístico-C (AUROC) y el índice Harrell c. El estadístico-C es la medida más usada y reportada para la discriminación de los modelos de predicción CV. El estadístico-C refleja la capacidad del índice para discriminar entre individuos que presentan o no presentan eventos. En otras palabras, expresa la probabilidad de que un caso (evento) elegido al azar tenga un índice de riesgo superior a un no-caso (sin evento) elegido también al azar. (5) El índice de Harrell es otra herramienta estadística similar para comparar la discriminación de un modelo, pero permite agregar la variable tiempo de seguimiento, que mide la capacidad de este para asignarles un alto riesgo a individuos con corto tiempo con respecto al evento. (25, 26) La *calibración* fue analizada a través de la comparación de eventos predichos y observados por quintilo de riesgo. A su vez, se calculó la pendiente β de regresión lineal para las estimaciones, donde valores cercanos a 1 indican mejor calibración del modelo.

Para el cálculo de la sensibilidad y especificidad, las guías americanas sugieren el uso del punto de corte de 7,5% de riesgo a 10 años. Dado que el tiempo de seguimiento de la presente cohorte es menor, se estimó dicho punto de corte como el 3% de riesgo. Dicha adaptación se realizó a través de la siguiente fórmula: 1 – Exp (-1 * incidencia promedio anual de eventos * tiempo de seguimiento para en el percentilo 95% de seguimiento la cohorte). La sensibilidad fue calculada como verdaderos positivos (VP)/ (VP + falsos negativos) * 100. La especificidad fue calculada como verdaderos negativos (VN) / VN + falsos positivos) *100.

Consideraciones éticas

Este estudio fue realizado siguiendo las guías de protección de los derechos de personas que participan voluntariamente en estudios de investigación. Todos los participantes de la cohorte CESCAS firmaron un consentimiento informado que incluye la autorización para el uso de los datos para análisis secundario. El protocolo de la cohorte fue aprobado por comités de ética de todos los centros participantes en Argentina, Chile y Uruguay.

RESULTADOS

Seguimiento de la cohorte CESCAS

Luego de excluir aquellos participantes con antecedentes de enfermedad CV en la evaluación basal de la cohorte y los casos sin disponibilidad de mediciones bioquímicas basales completas, se consideraron para al presente análisis 6364 participantes. Al momento del análisis de la presente base de datos, la mediana del tiempo de seguimiento fue de 2,2 años, con un rango intercuartilo de 1,9 a 2,8 años. Fueron incorporados al análisis 60 eventos CV totales, como primer evento incidente (21 anginas e infartos agudos de miocardio, 15 accidentes cerebrovasculares, 10 insuficiencias cardíacas, 2 revascularizaciones y 12 muertes CV).

Parámetros de validación externa

La Tabla 2 presenta los parámetros de discriminación para las ecuaciones evaluadas ordenadas alfabéticamente. La Tabla 3 resume los parámetros de calibración analizados. La Tabla 4 muestra los valores de sensibilidad y especificidad para la detección de individuos con elevado RCV.

DISCUSIÓN

Este estudio evaluó parámetros de validación externa de ecuaciones de estimación de RCV en una cohorte del Cono Sur de Latinoamérica. Si bien con los datos actua-

Tabla 2. Parámetros de discriminación evaluados

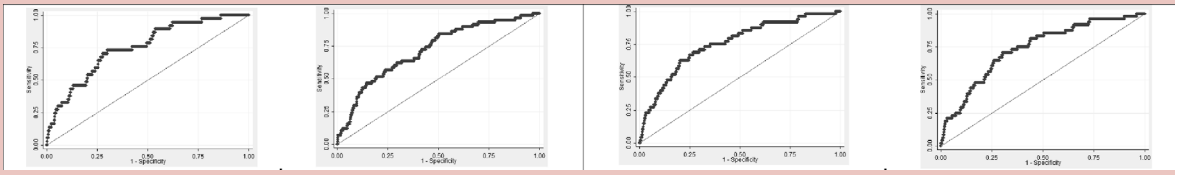
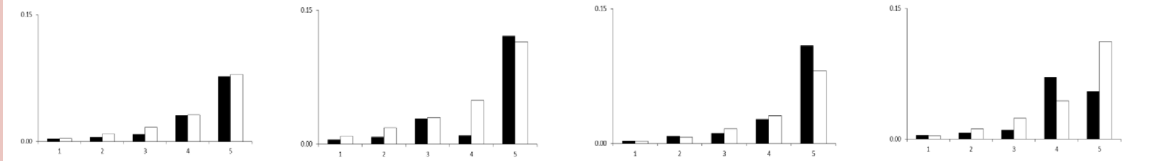
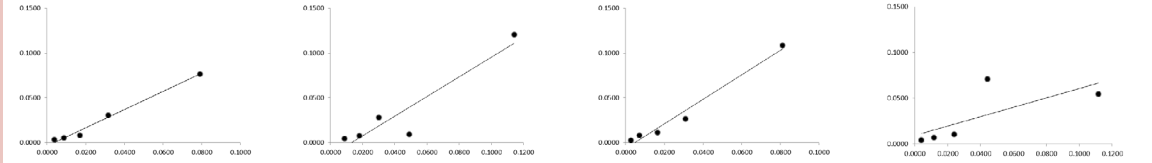
Ecuación	Cuore	Framingham	Globorisk	Pooled Cohort Studies Equations
Curva ROC				
Estadístico-C	0,751	0,719	0,753	0,736
Hanell C	0,752	0,722	0,736	0,743

Tabla 3. Parámetros de calibración evaluados

Ecuación	CUORE	Framingham	Globorisk	Pooled Cohort Studies Equations
Riesgo observado (■) *vs.* estimado (□) por quintilos de riesgo				
Regresión lineal riesgo observado *vs.* estimado				
Pendiente β	y = **1,012x** – 0,0036	y = **1,0956x** – 0,014	y = **1,3718x** – 0,0066	y = **0,5103x** + 0,0095

	Cuore	Framingham	Globorisk	Pooled Cohort Equations
Sensibilidad	73%	81%	75%	75%
Especificidad	69%	51%	60%	58%

Tabla 4. Sensibilidad y especificidad para la identificación de elevado RCV

les de seguimiento de la cohorte CESCAS, no se observan diferencias significativas al comparar las ecuaciones de riesgo seleccionadas entre sí, debemos destacar que CUORE, Framingham y Globorisk tuvieron los mejores parámetros globales de predicción en esta población.

Según lo publicado en la bibliografía, raramente las curvas ROC superan el valor de 0,8 (27) en análisis de validación de este tipo. En este estudio, todas las curvas superaron el valor de 0,7 en la cohorte CESCAS; Globorisk y CUORE fueron las ecuaciones con estadístico-C más altos. A su vez, los valores de Harrell C son también similares entre ellos. En lo que se refiere al grado de acuerdo entre los valores observados y los valores predichos por los modelos (calibración), CUORE, Globorisk y Framingham son las ecuaciones con mayor acuerdo en la comparación por quintilos de riesgo y valores de coeficiente β más cercanos a 1, mientras que la Pooled Cohort Studies Equations de AHA muestra inestabilidad del modelo en los quintilos de mayor riesgo con el valor de coeficiente β más distante de 1. En lo que respecta a la sensibilidad y especificidad, para la detección de individuos con elevado riesgo cardiovascular, las cuatro ecuaciones mostraron valores similares; la ecuación de Framingham fue la que mostró el valor más elevado para sensibilidad y CUORE para especificidad.

Ciertas observaciones y limitaciones deben ser mencionadas sobre las conclusiones de este estudio: 1) el tiempo de seguimiento actual de la cohorte CESCAS no permite un análisis de predicción a largo plazo, sin embargo, todos los análisis realizados en este estudio fueron ajustados a la sobrevida según el tiempo de seguimiento; 2) análisis posteriores contarán con un mayor número de eventos CV y permitirán incorporar en la comparación ecuaciones que evalúan exclusivamente mortalidad CV como SCORE; y 3) para la evaluación de la ecuación de Framingham no se tuvieron en cuenta los casos de claudicación intermitente dado que no fueron relevados en la cohorte.

Entre las fortalezas de este estudio podemos resaltar que, primero, a nuestro entender no se ha publicado previamente otro análisis de validación externa de ecuaciones de riesgo CV en población general del Cono Sur de Latinoamérica; segundo, se realizó la calibración de cada una de las ecuaciones para el riesgo basal de la población de la cohorte CESCAS utilizando los datos de prevalencia los factores de riesgo, esto último no es posible cuando no se cuenta con datos individuales a nivel poblacional y permite una adaptación más precisa de la ecuación en la población para la cual se la está estudiando; (27) y, tercero, se realizaron análisis independientes para cada ecuación teniendo en cuenta los eventos finales que evalúan y el rango etario para el cual fueron diseñadas.

El trabajo actual que se realiza en la cohorte CESCAS no solo permitirá incrementar la complejidad de los análisis de validación externa de las ecuaciones desarrolladas, sino que también permitirá la elaboración de un propio modelo de predicción de riesgo regional y la valoración de otro tipo de variables de predicción no convencionales como biomarcadores de inflamación o aterogénicos (PCR, lipoproteína A).

CONCLUSIONES

Las ecuaciones de predicción de riesgo evaluadas mostraron parámetros de predicción de riesgo similares. Las ecuaciones CUORE, Framingham y Globorisk fueron las que mejores parámetros presentaron. Estos resultados representan una primera aproximación para la elección del modelo de predicción más adecuado para nuestra población. Futuros puntos de corte de la cohorte CESCAS con mayor tiempo de seguimiento y mayor cantidad de eventos permitirán mejorar la clasificación de RCV a nivel poblacional sobre la base de la evidencia proveniente de datos de nuestra región.

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ORIGINAL ARTICLE

External Validation of Cardiovascular Risk Scores in the Southern Cone of Latin America: Which Predicts Better?

Validación externa de ecuaciones de riesgo cardiovascular en el Cono Sur de Latinoamérica: ¿cuál predice mejor?

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ABSTRACT

Background: Inaccurate estimates of demographic cardiovascular risk may lead to an inadequate management of preventive medical interventions such as the use of statins.
Objectives: The aim of this study was to evaluate the external validity of cardiovascular risk equations in the general population of the Southern Cone of Latin America.
Methods: Equations including variables evaluated in the CESCAS cohort study and that estimate overall cardiovascular mortality (CUORE, Framingham, Globorisk and Pooled Cohort Studies) were assessed. For each equation, an independent analysis was performed taking into account the cardiovascular events originally considered. Discrimination of each equation was evaluated through C-statistic and Harrell's C-index. To assess calibration, a graph was built for each equation with the proportion of observed events vs. the proportion of estimated events by risk quintiles and the β slope of the resulting linear regression was calculated. Sensitivity and specificity were determined for the detection of people at high cardiovascular risk.
Results: The median follow-up time of the cohort at the time of the analysis was 2.2 years, with an interquartile range of 1.9 to 2.8 years. Sixty cardiovascular events were incorporated into the analysis. All C-statistic and Harrell's-C index values were greater than 0.7. The value of the β slope farthest from 1 was that of the Pooled Cohort Studies score.
Conclusions: Although the external validation parameters evaluated were similar, CUORE, Globorisk and the Framingham equations showed the best global performance for cardiovascular risk estimation in our population.

Key words: Cardiovascular disease - Risk factors, risk assessment, prevention.

RESUMEN

Introducción: La estimación inexacta del riesgo cardiovascular poblacional puede llevar a un manejo inadecuado de las intervenciones médicas preventivas, como, por ejemplo, el uso de estatinas.
Objetivo: Evaluar la validez externa de ecuaciones de predicción de riesgo cardiovascular en población general del Cono Sur de Latinoamérica.
Material y métodos: Se evaluaron ecuaciones que incluyen variables evaluadas en el estudio CESCAS y que predicen tanto morbilidad como mortalidad cardiovascular global (CUORE, Framingham, Globorisk y Pooled Cohort Studies Equations). Para cada ecuación se realizó un análisis independiente en el que se tuvieron en cuenta los eventos cardiovasculares relevados. Se evaluó la discriminación de cada ecuación a través del cálculo del estadístico-C y el índice Harrell C. Para evaluar la calibración se graficó la proporción de riesgos observados vs. estimados por quintilos de riesgo para cada ecuación y se calculó la pendiente β de regresión lineal para las estimaciones. Se calculó sensibilidad y especificidad para la detección de personas con elevado riesgo cardiovascular.
Resultados: La mediana del tiempo de seguimiento de la cohorte al momento del análisis es de 2,2 años, con un rango intercuartilo de 1,9 a 2,8 años. Se incorporaron a los análisis 60 eventos cardiovasculares. Todos los valores de estadístico-C y del índice de Harrell fueron superiores a 0,7. El valor de la pendiente β más alejado de 1 fue el de Pooled Cohort Studies Euations.
Conclusiones: Si bien los parámetros de validación externa evaluados fueron similares, CUORE, Globorisk y el índice de Framingham fueron las ecuaciones con mejores indicadores globales de predicción de riesgo cardiovascular.

Palabras claves: Enfermedad cardiovascular - Factores de riesgo - Evaluación del riesgo - Prevención

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Abbreviations

CV	Cardiovascular	**CVR**	Cardiovascular risk
CVD	Cardiovascular disease		

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death both in developed and in developing countries. Approximately 80% of deaths of CV origin occur in low and middle income countries (1, 2) The INTERHEART study showed that nine measurable and potentially modifiable risk factors are responsible for 90% of acute myocardial infarctions. (3) Most of these CV risk (CVR) factors also represent the main causes of disease burden worldwide. (4) It is critical for developing countries to improve their ability to detect individuals at high CVR in order to benefit from more intense medical interventions.

In recent years, the estimation of CVR has assumed a central role in CV primary prevention, and research in the field of risk prediction has become subject of profound study. (5) The estimation of future CVR not only aids global clinical management as basis for individual therapeutic decision-making but also as a tool to evaluate the risk profile at the population level. (6) Decisions in CV prevention should be adopted after an adequate estimation of CVR; for example, medical treatment with statins in individuals at high CVR. (7) In turn, the calculation of CVR is not only an essential support tool for clinical decision-making, but also aids with the communication and diffusion of information to patients. (5)

Cardiovascular risk prediction scores are practical, easy to use tools at the level of primary care. Most models of CVR prediction have been built in developed countries using databases with different sociodemographic, epidemiological and nutritional realities than those found in the South Cone of Latin America regions. (5) In this context, inaccurate risk prediction may lead to inadequate onset of medical interventions in individuals at lower real risk than that predicted by equations created in different populations. (8, 9)

The aim of this study was thus to evaluate the external validity (calibration, discrimination, sensitivity and specificity) of CVR prediction equations built in developed countries, in the first follow-up data of the Center of Excellence in Cardiovascular Health for South America (CESCAS) cohort, a representative general population sample of four cities in the South Cone of Latin America (Argentina, Chile and Uruguay). To our knowledge, this is the first study that evaluates and compares different CVR prediction equations in populations belonging to the South Cone of Latin America. (9-11).

METHODS

Selected prediction equations

The selection of CVR prediction equations was based on models presented in the 2016 European guidelines on CVD prevention in clinical practice. (12) The equations incorporated for the analysis were selected following two steps: Firstly, prediction models whose variables had all been evaluated in the Southern Cone of Latin America CESCAS cohort were included and then, equations predicting only CV mortality or coronary events were finally excluded. The models evaluated were: ASSIGN-SCORE, (13) QRISK1 (14) & QRISK2 (15), SCORE, (16) PROCAM, (17) Pooled Cohort Studies Equations, (18) Framingham, (19) CUORE (20) and Globorisk. (21). Equations selected for evaluation corresponded to the last four risk models. Figure 1 depicts the selection process and Table 1 describes the final events predicted by these equations, the variables included in the models and the age ranges evaluated.

The CESCAS cohort

The details of the analysis and sampling method of the CESCAS cohort study have been previously published. (22-23). Essentially, CESCAS is a prospective cohort study including

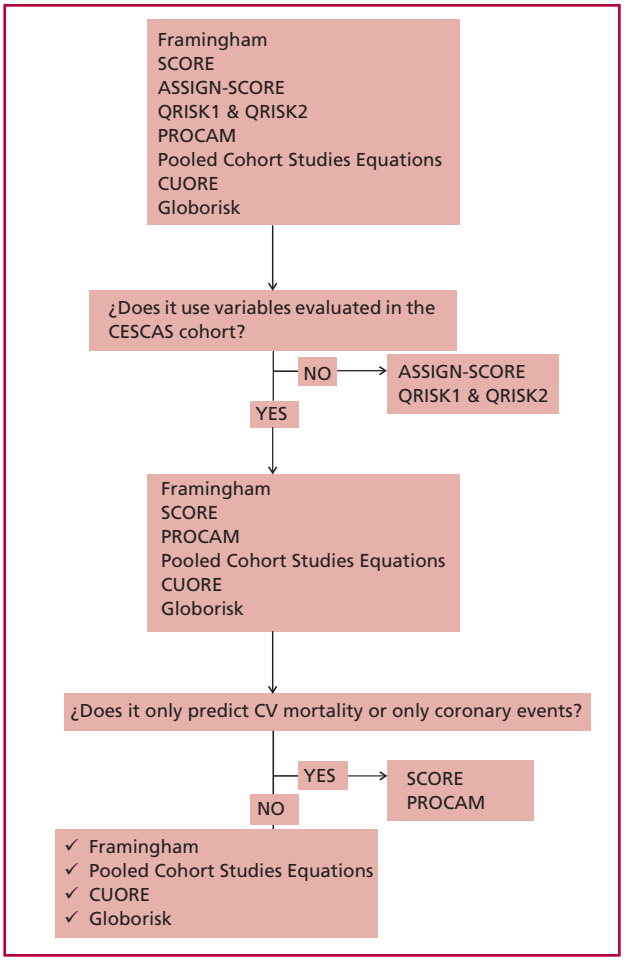


Fig. 1. Selection process of cardiovascular risk equations

Table 1. Characteristics of the models evaluated[¥]

	CUORE	Framingham	Globorisk	Pooled Cohort Studies Equations
Variables included in	Sex	Sex	Sex	Sex
the models	Age	Age	Age	Age
	Total cholesterol	Total cholesterol	Total cholesterol	Total cholesterol
	HDL-C	HDL-C	----------	HDL-C
	SMK	SMK	SMK	SMK
	SBP	SBP	SBP	SBP
	----------	DBT	DBT	DBT
	Antihypertensive treatment	Antihypertensive treatment	----------	Antihypertensive treatment
Age range	35-69	35-69	35-69	35-69

[¥] SMK: Smoking. SBP: Systolic blood pressure. DBT: Diabetes. HDL-C: HDL-cholesterol

7,524 adults (3,165 men and 4,359 women) from 35 to 74 years of age, recruited between December 2010 and December 2012. The sample originates from polystage sampling representative of the general population of four cities of the Southern Cone of Latin America: Bariloche and Marcos Paz (Argentina), Temuco (Chile) and Canelones (Uruguay). The global response rate was 73.4% and was similar in men and women across cities.

Study data were collected during a home visit and in another visit to a medical center. Socio-demographic information (age, sex, education and occupation) was obtained during the home survey. Anthropometric measurements were obtained by certified, trained staff using standardized protocols and techniques. Blood pressure was measured with the participant seated after a 5-minute rest, using a standard mercury or aneroid sphygmomanometer, and the average of three readings was considered for the analysis. Body weight, height and waist circumference were measured twice during the evaluation, and their average was used in all the analyses.

A fasting blood sample was withdrawn to assess lipoproteins, creatinine and blood sugar levels. The fasting interval was verified before blood withdrawal and no blood sample was taken if fasting was below 10 hours. Standard methods were used to determine blood glucose, total cholesterol, HDL-cholesterol, triglycerides and creatinine. LDL-cholesterol concentration was calculated using Friedewald's equation when triglycerides were <400mg/dL. (24) Diabetes was defined as blood sugar levels ≥ 126 mg/dL and/or self-reported history of diabetes and/or its current treatment with insulin or oral anticoagulants.

Cardiovascular events (angina, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, coronary artery, carotid or peripheral revascularization procedure, heart failure and sudden death) in this first follow-up evaluation were confirmed by a specialist in internal medicine or a cardiologist after verifying the event-specific record. Of importance, the CESCAS cohort did not reveal intermittent claudication, one of the Framingham equation endpoints.

Statistical analysis: external validation of the models

The regression coefficients of the original publications were obtained for each selected model. Together with these coefficients, all the equations were recalibrated to the CESCAS population with the following exponential equation: (19)

$$\hat{p} = 1 - S_0(t)^{\exp(\sum_{i=1}^{p} \beta_i x_i - \sum_i^p \beta_i \bar{x}_i)}$$

where S_0 (t) is survival at the specific follow-up time; β_i are the estimated coefficients of regression (Log hazard ratio); X_i is the specific value of each risk factor considered for the equation; $\bar{X}_i$ refers to the mean value of each risk factor in the CESCAS population at baseline and p corresponds to the number of risk factors for each equation.

A different "endpoint" variable for each equation was created in the database (Table1), specifically including the events for which they were designed as prediction tools.

The discrimination of each equation was assessed through the calculation of the C-statistic (Area under the ROC curve, AUROC) and Harrell's C-index. The C-statistic is the most commonly used measurement for the discrimination of CV prediction models. It reflects the ability of this index to discriminate between individuals presenting or not events. Namely, it expresses the probability that a randomly selected case (event) has a risk score above a randomly selected non-case (without event). (5) Harrell's C-index is another similar statistical tool to compare the discrimination of a model, but allows the addition of follow-up time, which measures its capacity to assign high risk to individuals with short time to the event. (25, 26) Calibration was analyzed comparing predicted and observed events per risk quintile. In addition, the β slope of the linear regression estimates was calculated, where values close to 1 indicate better model calibration.

For the calculation of sensitivity and specificity, the American guidelines suggest a cut-off point of 7.5% risk at 10 years. Since the follow-up time of the present cohort is lower, the cut-off point was estimated as 3% risk. This adaptation was performed using the following formula: 1 – Exp (-1*average annual incidence of events*follow-up time for the 95% cohort percentile). Sensitivity was calculated as true positives (TP)/(TP + false negatives) *100. Specificity was calculated as true negatives (TN)/TN + false positives) *100.

Ethical considerations

This study was performed following data protection rights guidelines of people who voluntarily participated in the study. All CESCAS cohort participants signed an informed consent including the authorization of data use for secondary analysis. Cohort protocol was approved by the Ethics

Committees of all the centers participating in Argentina, Chile and Uruguay.

RESULTS

Follow-up of the CESCAS cohort

After the exclusion of participants with history of CVD at baseline cohort evaluation, and cases without available complete baseline biochemical tests, 6,364 participants were included in the study. At the time of analysis of the present database, median follow-up was 2.2 years, interquartile range 1.9-2.8 years. A total of 60 primary CV events occurred during that interval: 21 anginas and acute myocardial infarctions, 15 strokes, 10 heart failures, 2 coronary artery revascularization procedures and 12 CV deaths.

External validation parameters

Table 2 presents the discrimination parameters alphabetically ordered. Table 3 summarizes the calibration parameters analyzed and Table 4 shows the sensitivity and specificity values for the detection of individuals with elevated CVR.

DISCUSSION

The study assessed external validation parameters of equations estimating CVR in a Southern Cone of Latin America cohort. Even though current follow-up data of the CESCAS cohort did not provide significant differences among selected equations, we should point out that CUORE, Framingham and Globorisk scores had the best prediction parameters in this population.

According to the literature, ROC curves rarely exceed 0.8 values (27) in this type of validation analyses. In this study, all the curves in the CESCAS cohort were above 0.7, with Globorisk and CUORE presenting the highest C-statistics. Moreover, Harrell's C-index was similar among the different equations. Assessment of the degree of agreement between observed and pre-

Table 2. Discrimination parameters evaluated

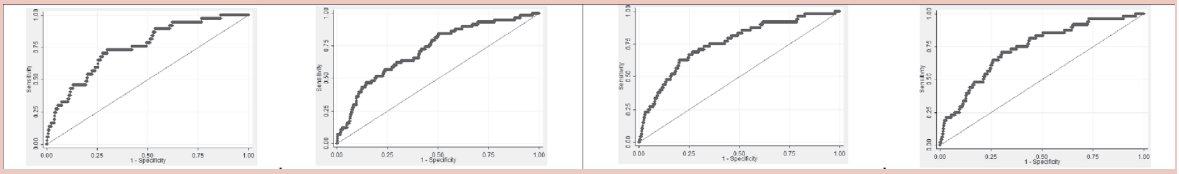
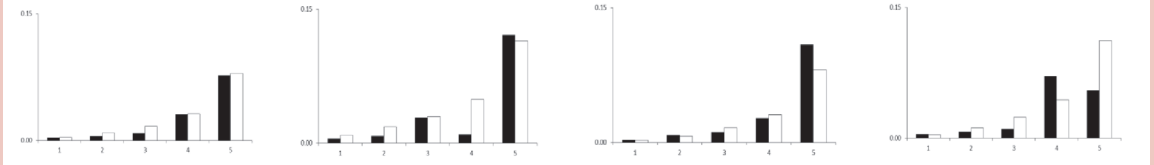
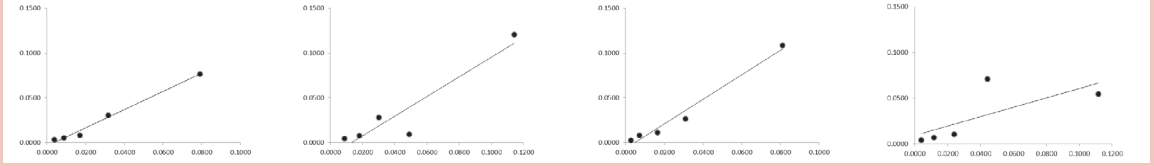
Equatio	CUORE	Framingham	Globorisk	Pooled Cohort Studies Equations
ROC curve				
C-statistic	0.751	0.719	0.753	0.736
Harrell's C index	0.752	0.722	0.736	0.743

Table 3. Calibration parameters evaluated

Equatio	CUORE	Framingham	Globorisk	Pooled Cohort Studies Equations
Observed (■) vs. estimated (□) risk per risk quintiles				
Linear regression of observed vs. estimated risk				
β slope	y = 1.012x – 0.0036	y = 1.0956x – 0.014	y = 1.3718x – 0.0066	y = 0.5103x + 0.0095

	CUORE	Framingham	Globorisk	Pooled Cohort Equations
Sensitivity	73%	81%	75%	75%
Specificity	69%	51%	60%	58%

Table 4. Sensitivity and specificity for the identification of high cardiovascular risk

dicted model values (calibration) showed that CUORE, Globorisk and Framingham were the equations with highest accordance in the comparison per risk quintiles and with β coefficient closer to 1, whereas the AHA Pooled Cohort Studies Equations showed model instability in the higher risk quintiles with β coefficient farther from 1. The four equations showed comparable sensitivity and specificity to detect individuals at elevated CV risk, the Framingham equation evidencing the highest value for sensitivity and CUORE for specificity.

Certain observations and limitations should be mentioned about the conclusions of this study: 1) the current follow-up time of the CESCAS cohort does not allow a long-term prediction analysis; however, all the analyses performed in the study were adjusted to survival according to the follow-up time; 2) future analyses will have a greater number of CV events, allowing the incorporation of equations evaluating exclusively CV mortality such as the SCORE model; and 3) intermittent claudication cases were not considered for the evaluation of the Framingham equation, as they were not recorded in the cohort.

Among the strengths of this study, we should first mention that, to our understanding, no other external validation analysis of CVR equations has been previously published in the general population of the Southern Cone of Latin America; second, calibration of each equation for baseline risk of the CESCAS cohort population was performed using prevalent risk factor data, which would not have been possible without individual population data for a more accurate adaptation of the model to the population under the study (27), and; third, independent analyses were performed for each equation taking into account the final events they evaluate and the age range for which they were designed.

Current work in the CESCAS cohort will not only increase the complexity of external validation analyses of the equations developed, but will also allow the construction of a proper regional prediction model and the evaluation of other types of non-conventional prediction variables as inflammation or atherogenic biomarkers (PCR, lipoprotein A).

CONCLUSIONS

Risk prediction equations evaluated in the study showed similar risk prediction parameters and CUORE, Framingham and Globorisk equations presented the best parameters. These results represent a first approximation for the selection of the most adequate prediction model for our population. Future cut-off points of CESCAS cohort with longer follow-up and higher number of events will improve the CVR classification at the population level based upon the evidence resulting from data of our region.

Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

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EDITORIAL

2017 Dr. Pedro Cossio Foundation Award

Premio Fundación Dr. Pedro Cossio 2017

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The Scientific Committee of the 43rd Argentine Congress of Cardiology selected 4 works to contend for the 2017 Dr. Pedro Cossio Foundation Award. Continuing with the tradition installed 31 years ago, we shall make brief comments about the works selected.

The winning work was:

"External Validation of Cardiovascular Risk Equations in the Southern Cone of Latin America: Which Predicts Better?", by Pablo E. Gulayin, Goodarz Danaei, Laura Gutierrez, Rosana Poggio, Jaqueline Ponzo, Fernando Lanas, Adolfo Rubinstein, Vilma Irazola. Institute for Clinical Effectiveness and Health Policy (IECS), Argentina; Chair of Public Health, School of Medicine, UNLP; Harvard T.H. Chan School of Public Health, United States; Universidad de la República, Uruguay; Universidad de la Frontera, Chile;National Ministry of Health, Argentina.

The Center of Excellence in Cardiovascular Health (CESCAS) conducts an important prospective population-based cohort study. Coordinated by the Institute for Clinical Effectiveness and Health Policy (IECS), the study is supported by the National Heart, Lung and Blood Institute (NHLBI, United States) and other important international institutions and universities. The study started in 2009 and included 7,524 men and women between 35 and 74 years. The population was recruited in 4 locations of the Southern Cone of Latin America: Marcos Paz and Bariloche (Argentina), Pando (Uruguay) and Temuco (Chile).

The aim of this study was to investigate the prevalence and incidence of risk factors for chronic noncommunicable diseases as cardiovascular disease, chronic obstructive pulmonary disease and cancer in the general population and make a longitudinal record of events. Since the beginning of the project, this group has published numerous articles in international peer-reviewed journals. (1)

The estimation of global cardiovascular risk constitutes a crucial step in primary prevention, as it represents an adequate tool to decide the intensity of the measures to consider in each particular case. Several risk scores in different populations worldwide have been published in the last years. (2) Yet, none of them has been adapted to the population of the Southern Cone of America. The aim of this study was to evaluate the external validity of cardiovascular risk prediction equations built in developed countries and compare the applicability of four known scores (Pooled Cohort Studies Equations, Framingham, CUORE and Globorisk) in the Argentine population. These scores were selected as they included the same variables used in the CESCAS cohort and considered the total number of coronary events as final endpoints.

The information was obtained during household visits and included socio-demographic data, anthropometric measurements and clinical variables. The following cardiovascular events were considered: angina, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, myocardial or peripheral revascularization, heart failure and sudden death.

The sensitivity, specificity, and prediction of occurrence or non-occurrence of events by means of the C-statistics (area under the ROC curve) was evaluated for each score, as well as the calibration analyzed through the comparison between predicted and observed events. After a median follow-up of 2.2 years, a total of 60 cardiovascular events were recorded (21 cases of angina and myocardial infarction, 15 cases of stroke, 10 of heart failure, 2 revascularizations and 12 cardiovascular deaths).

The Framingham risk score showed the highest sensitivity (81%) and the CUORE score presented the highest specificity (69%). All the curves in the CESCAS cohort had a C-statistic value >0.7. The calibration between predicted and observed values was higher for the CUORE, Globorisk and Framingham risk scores than for the Pooled Cohort Studies Equations.

There is evidence that risk equations developed in a given population are not adequately applicable to others with different genetic load, lifestyle or diet (3-4). The SAC Consensus on Cardiovascular Prevention recommends the use of WHO prediction risk charts for the sub-region America B as the most accurate tool at present. (2) CESCAS is the first longitudinal population-based study designed to evaluate the different cardiovascular risk prediction equations in the Southern Cone of America. Probably, it will allow in time to develop a specific model for our region, which may also include novel predictive variables such as atherogenic (lipoprotein A) or genetic biomarkers.

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President of the Jury of the Dr. Pedro Cossio Foundation Award

Despite the short follow-up period and the small number of events collected to make robust conclusions, the Jury of the 2017 Dr. Pedro Cossio Foundation Award unanimously considered that this work deserved to be the winner for its excellent design, meticulous development and originality of conclusions.

The other three works were:

"Increased Pulmonary Vascular Resistance in Heart Transplantation Candidates Predicts Postoperative Right Ventricular Failure: Is This Reason Strong Enough to Contraindicate Transplantation?", by Ezequiel Espinoza; Ignacio Martin Bluro; Santiago Sáncuez Bustamente; Rodolfo Pizarro; Ricardo Marenchino; Marcela Proietto; Norberto Vulcano; Cesar Antonio Belzitti.

In this study, the investigators of the Instituto de Medicina Cardiovascular, Hospital Italiano de Buenos Aires, studied 93 patients undergoing heart transplantation between January 2012 and April 2017. The aim of this investigation was to determine the preoperative threshold value of pulmonary vascular resistance above which 30-day mortality (primary endpoint) or postoperative right ventricular (RV) dysfunction (secondary endpoint), defined as evidence of RV dysfunction on echocardiography associated with requirement of inotropic drugs or duration of inotropic support and mechanical ventilation, develop. The value of pulmonary artery pressures, pulmonary capillary wedge pressure and pulmonary vascular resistance expressed in Wood units (WU) were obtained during the last cardiac catheterization before transplantation. Mortality at 30 days was 5.3% and was only associated with inotropic requirement for >48 hours. The incidence of RV dysfunction in the immediate postoperative period was 22.6% and was associated with all the hemodynamic variables of pulmonary pressures and vascular resistance and with the echocardiographic variables of RV function.

Multivariate analysis revealed that tricuspid annulus plane systolic excursion (TAPSE)-to-pulmonary artery systolic pressure (PASP) ratio measured by Doppler echocardiography showed the best performance among all the hemodynamic and echocardiographic variables. A TAPSE/PASP ratio of 0.26 mm/mm Hg had an area under the ROC curve of 0.84 with very good calibration according to the Hosmer-Lemeshow test. Only this ratio presented an independent association with RV dysfunction (OR >10; 95% CI, 2.2->100; p=0.03). Pulmonary vascular resistance was the variable that best predicted postoperative RV dysfunction, and adequately classified 80% of the patients. Early mortality was 14.3% in patients with PVR >5.6 WU vs. 3.8% in those with PVR <5.6 WU (OR 4.2; 95% CI, 0.64-28; p=0.13).

Pulmonary hypertension is common in patients on the waiting list for heart transplantation and is sometimes a limiting condition for transplantation associated with adverse outcome, particularly due to acute RV dysfunction. The extensive waiting list and the difficulties related with organ procurement require allocation of the explanted hearts to candidates who are expected to benefit from the intervention. Thus, reliable criteria should be established for decision-making. Although the primary endpoint was not achieved, the authors of this paper suggest this cut-off value. This limitation could be explained by the retrospective design of this single-center study with a limited number of patients and few events.

"Prognostic Value of the Size of Necrosis in Patients with Ischemic Ventricular Dysfunction Undergoing Revascularization", by Santiago del Castillo, Diego Perez de Arenaza , Landy Rodriguez, Federico Marcos, Juan Benger, Mariano Falconi, Marcelo Petrani, Arturo Cagide, Ricardo Garcia Monaco, Cesar Belziti.

In another study from Hospital Italiano de Buenos Aires, 35 patients with coronary artery disease with ischemic left ventricular dysfunction (ejection fraction ≤45%) undergoing myocardial revascularization (surgery or percutaneous coronary intervention) were studied. Before revascularization, myocardial viability was analyzed by cardiac magnetic resonance imaging (MRI) with quantification of the size of myocardial necrosis by late gadolinium enhancement (LGE). The aim of the study was to assess the prognostic value of quantifying the size of myocardial necrosis by LGE, and to compare it with viability criteria by cardiac MRI (necrosis involving <50% of wall thickness).

The primary endpoint was overall mortality or cardiac transplantation after a mean follow-up of 3 years. The median number of viable segments was 12 and mean necrotic mass was 46±6 g. The primary endpoint was achieved in 28.5% of the cases. At univariate analysis, the number of viable segments and the size of myocardial necrosis in grams and indexed by body surface area was associated with the primary endpoint. However, the analysis of the ROC curve showed that a size of 28 g/m2 had the best discrimination ability, with an area under the curve of 0.69 (95% CI, 0.45-0.92), with a sensitivity of 70% and a specificity of 84% for the primary endpoint. Multivariate Cox proportional hazard analysis demonstrated that age and indexed necrosis size were the only variables associated with the primary outcome (HR 1.16; 95% CI, 1.02-1.33 p=0.02 and HR 1.06; 95% CI 1.01-1.11 p=0.007, respectively).

Several observational studies and a meta-analysis published in the past decade suggested that patients with ischemic ventricular dysfunction and myocardial viability detected on functional stress imaging studies had better outcome and higher survival rate after revascularization. On the contrary, this benefit was not achieved by patients with necrotic dysfunction. (5) The pathophysiological basis of this hypothesis was that reperfusion of necrotic segments without viable contractile tissue would supply blood flow to areas without functional recovery. This would not happen if areas with viable myocardial tissue were revascularized. This statement was questioned by the

STICH (Surgical Treatment for IschemiC Heart Failure) study, which compared myocardial revascularization with medical treatment and did not identify patients with different survival rates. (6) Despite being conducted in a single center with a reduced number of cases, this paper presents a new hypothesis that highlights the importance of the total volume of the necrotic mass over the number of viable ischemic segments as a predictor of success achieved by revascularization, Yet, this hypothesis needs to be validated by additional larger prospective multicenter studies.

"Validation and Comparison of Two Simple Models of Risk Stratification in Patients with ST-Segment Elevation Acute Myocardial Infarction in Argentina", by Lucrecia M. Burgos, Cristian M. Garmendia, Elián F. Giordanino, Casandra L. Godoy Armando, Ignacio M. Cigalini, Sebastián García Zamora. Ricardo Iglesias, Juan P. Costabel

This is a new publication of the fruitful production of the Argentine Council of Cardiology Residents (CONAREC). The aim of this study was to validate two international risk scores of patients hospitalized due to ST-segment elevation acute myocardial infarction in Argentina, included in the CONAREC XVII registry. (7) The scores mentioned were the Simple Risk Index (SRI) from the United States published in 2001 (8) and the Portuguese Registry of Acute Coronary Syndromes (ProACS) from Portugal, published in 2017. (9) Several scores have been developed for risk stratification of acute coronary syndrome patients with the goal of implementing diagnostic and therapeutic measures (medical treatment or invasive procedures) according to the risk calculated. Some scores are complex and include a great number of sophisticated variables, as biochemical, echocardiographic or angiographic parameters, and are therefore impractical for rapid bedside decision-making. These two scores were selected because they are simple and have adequate efficiency demonstrated by external validations. The SRI includes age, heart rate and systolic blood pressure. The ProACS risk score evaluates age, systolic blood pressure, ST-segment elevation and Killip and Kimball index.

A total of 694 patients from 45 centers were included. The primary endpoint, in-hospital mortality, occurred in 8.78% of patients. Both scores showed good discrimination to predict the primary endpoint (AUC 0.83; 95% CI, 0.78-0.88, p=0.001 for the SRI, and 0.78; 95% CI 0.71-0.86, p=0.001 for the ProACS risk score). In both cases, the calibration was satisfactory according to the Hosmer-Lemeshow test. Although all the patients with ST-segment elevation acute myocardial infarction require urgent reperfusion with thrombolysis or percutaneous coronary intervention, the use of these tools would be useful for risk stratification as they include simple variables that can be quickly collected at the first contact with the patient in order to adjust the decision-making process.

The jury of the 2017 Dr. Pedro Cossio Foundation Award was formed by the former presidents of the Argentine Society of Cardiology, Dr. Hugo Grancelli and Dr. Alvaro Sosa Liprandi, to whom I am grateful for their skilled and responsible participation.

CONFLICTS OF INTEREST

None declared.

(See authors' conflicts of interest forms on the website/Supplementary material).

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